REMARKS:

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claim 1-28 have been cancelled in favor of new Claims 29-37, the amendments being made in order to expedite prosecution. All of the current claims are directed to a monoclonal antibody which specifically binds human B7.1 antigen (CD80) which inhibit the binding of human B7.1 antigen to CD28, but which do not inhibit the binding of B7.1 antigen to CTLA-4, and compositions containing. All of the pending claims find basis in the original claims as well as the disclosure at pages 33-34 of the application, wherein the construction of primatized anti-B7.1 antibodies is described.

Turning now to the Office Action, the previous restriction requirement and the Election, with traverse, of monoclonal antibodies specific to B7.1 antigen is confirmed. Applicants further confirm their election of species, namely monoclonal antibodies specific to B7.1. The election of species requirement should now be moot as Applicants have limited the claims to monoclonal antibodies which specifically bind human B7.1 antigen. All of the newly-introduced claims read upon the elected subject matter.

Applicants further note the objection to the figures as being informal. Formal figures will be submitted upon indication that this application is otherwise allowable.

The objection to the trademark designations is also noted. Applicants respectfully advise that the trademark phrases have been capitalized in the application.

Claim 11 stands objected to under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description of the invention. Essentially, the basis of the rejection is that this claim requires specific monoclonal antibodies, the enablement which may require the availability of specific deposited cell lines. This rejection should be moot as the current claims are no longer directed to specific antibodies. Rather, the claims are generically directed to monoclonal antibodies which specifically bind human B7.1 antigen and which do not inhibit the binding of human B7.1 antigen to CTLA-4. In this regard, several monoclonal antibodies which meet this characteristic are exemplified in the subject application. Moreover, the enablement of these claims does not require deposit of a specific cell line as the amino acid and nucleotide sequences corresponding to these antibodies may be found in the figures submitted with this application. In particular, Figure 3, 3a and 3b contain the sequences of antibody 7C10, Figures 4a and 4b contain the sequences of antibody 7B6, and Figure 5a the sequence of antibody 16C10. Applicants further respectfully advise that the claims directed to the specific monoclonal antibodies were allowed in the parent application, i.e., U.S. Serial No. 08/487,550, filed June 7, 1995. Withdrawal of the previous §112 enablement rejection is therefore respectfully requested.

Previous Claims 11 and 26 further were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. None of these rejections should be applicable against the current claims. In particular, none of the current claims refer to specific antibodies, i.e., 16C10 or 7C10. Also, the previous objection to Claim 26 is moot as the recitation asserted to be unclear does not appear in any of the current pending claims.

Turning now to the prior art rejection, Claims 1-3, 6, 7, 9 and 14 stand rejected under 35 U.S.C. §102(b) as being anticipated by Linsley et al (*PNAS* 1990). The Examiner concludes that this reference teaches a monoclonal antibody specific to B7.1 antigen which anticipates the monoclonal antibodies which were set forth in previous Claims 1-3, 6, 7, 9 and 14. For example, the Examiner asserts that the antibody in the reference meets the claimed functional limitations because it is inhibitory at a concentration of 10 μg/ml, and because the current designation B7.1 is a synonym for the B7 antigen. This rejection is respectfully traversed to the extent it may be applicable to the claims as amended.

Applicants respectfully advise that all of the claims now include as an essential feature a monoclonal antibody that specifically binds human B7.1 antigen, which antibody inhibits the binding of B7.1 antigen to CD28, which antibody does not inhibit the binding of human B7.1 antigen to CTLA-4. Applicants have carefully reviewed the Linsley et al reference, however, it does not appear that this reference teaches or suggests an antibody

that meets this functional limitation. In particular, it would appear that the reference is directed to monoclonal antibodies that inhibit CD28-mediated adhesion, including monoclonal antibody BB-1, which is specific to the B-cell activation antigen B7. Also, the reference teaches some monoclonal antibodies against other major histocompatibility complex class 1 antigens. The specific monoclonal antibodies disclosed in the reference are identified in the materials and method section, which appears at page 5031 of the reference. Based on Applicants' review of the reference, it would appear that the only monoclonal antibody which specifically binds B7.1 antigen is BB-1. However, Applicants respectfully advise that this monoclonal antibody does not meet the limitations of the claimed invention.

In particular, this monoclonal antibody, which is a murine monoclonal antibody, while it apparently binds B7.1 antigen, inhibits the interaction of B7.1 antigen to CTLA-4. By contrast, the monoclonal antibodies of the claimed invention do not. The fact that BB-1 antibody inhibits such interaction may be appreciated upon review of the comparative results contained in Example 10 of the subject application. This Example contains competitive binding experiments which clearly demonstrate that the BB-1 antibody of Linsley et al completely blocked the binding of CTLA-4 Ig-biotin to B7.1 transfected CHO cells. By contrast, the monoclonal antibodies of the subject invention recognize a unique binding determinant on B7.1 which allows for normal CTLA-4 ligand binding and the generation of negative signals. As discussed in

further detail in the subject application, the monoclonal antibodies of the claimed invention are advantageous, vis-a-vis those of Linsley et al, because this type of interaction should enable the ability to block binding of B7.1 to CD28 receptors while still allowing the negative signalling function of CTLA-4 to occur uninhibited. This interaction should result in down regulation of the overall T-cell activation response regardless of the predominance of either TH1 or TH2 phenotypes.

Therefore, these antibodies should be well suited for use as therapeutics, in particular, for immunosuppression, e.g., in the treatment of autoimmune diseases, allergic disorders, prevention and treatment of graft-vs-host disease, bone marrow transplant and for the induction of host-tolerance to donor-specific aloe antigens. Based on the foregoing, withdrawal of the §102(b) rejection based on Linsley et al (*PNAS* 1990) is respectfully requested.

Claims 1-3, 6, 7, 9 and 14 further stand rejected under 35 U.S.C. §102(b) as being anticipated by Linsley et al, (*J. of Exp. Med.*, 1991). This reference also discloses a monoclonal antibody specific to the B-cell activation antigen B7, which purportedly co-stimulates T-cell proliferation and IL-2 mRNA accumulation. However, based on Applicants' review of the reference, it does not appear that Linsley et al teaches or suggests a monoclonal antibody having the claimed characteristics, namely, one which is capable of binding human B7.1 and which does not inhibit the binding of B7.1 antigen to CTLA-4. Based on Applicants' review

of the reference, it would appear that the only monoclonal antibodies disclosed are monoclonal antibody 9.3 and BB-1 which purportedly block T-helper cell-inducted Ig production by B-cells. These conditions are disclosed at page 728 of the reference under unpublished results. However, there is no indication that either of these antibodies exhibit the characteristics of the claimed monoclonal antibodies. In fact, there is evidence to the contrary in this application. As discussed above, Example 10 demonstrates that monoclonal antibody BB-1, unlike the claimed monoclonal antibodies, does inhibit the interaction of B7.1 antigen with CTLA-4. This is clearly demonstrated based on the competition binding experiments reported in Example 10, the results of which are contained in Figures 8 and 9. Also, the 9.3 antibody is specific to a different antigen, i.e., CD28.

Also, Linsley et al provides no suggestion to produce a monoclonal antibody having the claimed characteristics, namely one which is capable of specifically binding human B7.1 antigen and inhibiting the interaction of B7.1 antigen to CD28, but which antibody does not inhibit the interaction of B7.1 antigen with CTLA-4. Therefore, Applicants respectfully submit that the claimed monoclonal antibodies are also patentable over Linsley et al, *J. Exp. Med.*, 1991.

Claims 1-3, 6, 7, 9 and 14 further stand rejected under 35 U.S.C. §102(b) as being anticipated by Linsley et al, U.S. Patent 5,434,131, or U.S. Patent 5,521,288. These §102 rejections are discussed together as these patents contain very similar disclo-

sures. Linsley et al '131 relates to a method for regulating functional CTLA-4 positive T-cell interactions with B7 positive cells comprising contacting B7 positive cells with a B7 ligand which interferes with the reaction of B7 antigen with CTLA-4. Among the ligands disclosed to be suitable for inhibiting such interactions include monoclonal antibodies reactive with B7 antigen. This is apparent based on Col. 4, lines 60-65, of the patent. Also, at Col. 13, the patent teaches the use of anti-B7 monoclonal antibodies to B7 antigen to inhibit interactions of CD28-positive and CTLA-4 positive T-cells with B7 positive cells. In reviewing the patent disclosure, it would appear that the only anti-B7 monoclonal antibody exemplified is BB-1. However, this monoclonal antibody does not meet the functional limitations of the claimed invention. As discussed above, while this antibody specifically binds B7.1 antigen, it inhibits the interaction of B7.1 antigen with CTLA-4. Therefore, it does not anticipate the monoclonal antibodies of the claimed invention.

Moreover, Linsley et al provides no suggestion to produce a monoclonal antibody having the claimed characteristics, namely one which inhibits the interaction of B7.1 antigen with CD28, but which does not inhibit the interaction of B7.1 antigen with CTLA-4. Rather, Linsley et al merely contains a broad generic disclosure relating to the production of monoclonal antibodies specific to B7.1 but provides no specific teaching to produce monoclonal antibodies having the claimed binding characteristics. Moreover, Applicants respectfully submit that the patent would provide a

disincentive against producing monoclonal antibodies having the claimed binding characteristics given the patented claims which are limited to inhibiting interactions of B7 positive cells that interfere with the reaction of B7 antigen with CTLA-4. This is consistent with the fact that the only exemplified monoclonal antibody, i.e., BB-1, exhibits such functional characteristics. Therefore, Applicants respectfully submit that Linsley et al, U.S. Patent 5,434,131 does not anticipate the claimed invention.

Likewise, Linsley et al, U.S. Patent 5,521,288 also does not anticipate the monoclonal antibodies of the claimed invention. This reference also teaches monoclonal antibodies specific to B7 or CD28 fusion proteins and their use as therapeutics. Specifically, this patent exemplifies two different monoclonal antibodies, i.e., monoclonal antibody 9.3, which apparently specifically binds CD28, and BB-1 which specifically binds B7 antigen. Applicants have carefully reviewed this patent, however, it does not appear that any other monoclonal antibodies which bind B7 antigen are disclosed therein. Therefore, this patent likewise does not teach or suggest the monoclonal antibodies of the claimed invention. As discussed above and based on the comparative results contained in Example 11, the BB-1 antibody does not comprise the functional characteristics of the claimed monoclonal antibodies. Specifically, while it binds with B7.1 antigen, unlike the claimed monoclonal antibodies, it does inhibit the interaction of B7.1 antigen with CTLA-4. Also, this reference provides no teaching or suggestion to produce a monoclonal antibody capable

of binding B7.1 antigen which inhibits the binding of B7.1 antigen to CD28, but which does not inhibit the binding of B7.1 antigen to CTLA-4. In fact, the prior art provides no indication that such an antibody could even be obtained. Therefore, Applicants respectfully request that the anticipatory rejection based on Linsley et al '131 and '756 should also be withdrawn.

Finally, Claims 1-3, 6, 7, and 9-14 stand rejected under 35 U.S.C. §103 as being unpatentable over Linsley et al (*PNAS*, 1990), Linsley et al (J. Exp. Med., 1991), Linsley et al (U.S. Patent 5,434,131), or Linsley et al (U.S. Patent 5,580,756), in view of art-known procedures and motivation for producing recombinant antibodies, in particular relating to humanized, chimeric or primatized antibodies as acknowledged at pages 15-20 of the subject application, and Newman et al, *Biotechnology* 1992. This rejection is respectfully traversed to the extent it may be applicable to the claims as amended.

The Linsley et al references have all been discussed *supra* in the traversal of the §102 rejection based on these references. As discussed therein, none of these references teaches or suggests a monoclonal antibody having the claimed binding characteristics, namely one which specifically binds human B7.1 antigen which inhibits the interaction of B7.1 antigen with CD28, but which does not inhibit the interaction of B7.1 antigen with CTLA-4. Rather, the only exemplified antibody, BB-1, disclosed in the Linsley et al references, while it apparently binds B7.1 antigen, substantially inhibits the interaction of B7.1 antigen with CTLA-

4. By contrast, the claimed monoclonal antibodies do not inhibit such interaction.

As also discussed above, this is a significant distinguishing feature of the subject antibodies. Specifically, such antibodies will block the primary activation site between CD28 and B7.1 while will allowing the combined antagonistic effect on positive co-stimulation with an agonistic effect on negative signalling to occur unimpeded. This will provide a useful therapeutic approach for intervening in diseases, e.g., relapse forms of autoimmune diseases. Therefore, the monoclonal antibodies of the claimed invention block the binding of CD80 (B7.1) to CD28, preventing signals for T-cell activation, yet do not interfere with binding of CD80 (B7.1) to CTLA-4. As a result, these antibodies can be used to effectively inhibit IL2 production, T-cell proliferation and antibody production, i.e., by as much as one hundred percent.

As discussed above, none of the Linsley et al references teaches or suggests a monoclonal antibody exhibiting such properties. Rather, the monoclonal antibody of Linsley et al apparently binds to a distinct epitope and therefore inhibit the interaction of B7.1 antigen with CTLA-4. Therefore, unlike the claimed anti-B7.1 monoclonal antibodies, these monoclonal antibodies will interfere with B7.1/CTLA-4 negative signalling. This is potentially disadvantageous as CTLA-4 apparently has a role in negative signalling, facilitating a down-regulation of a immune response in the absence of repetitive antigen presentation.

However, the exact mechanism by which CTLA-4 mediates a negative signal is still under investigation.

The enhanced properties of monoclonal antibodies having the claimed binding characteristics may further be appreciated upon review of a manuscript which is to be published by the inventors. This reference, which is attached to Applicants' Reply, teaches the advantages of monoclonal antibodies specific to B7.1 which do not inhibit the interaction of this antigen with CTLA-4. As discussed therein, the antibodies according to the invention such antibodies effectively inhibit the co-stimulation signal delivered via B7.1/CD28 interaction without the potential of interfering with the B7.1/CTLA-4 negative signalling, and as a result, effectively inhibit IL2 production, T-cell proliferation and antibody production. Consequently, they provide useful therapeutics for treatment of diseases wherein immunosuppression is desirable. Therefore, the claimed invention is not taught by any of the Linsley et al references, separately or in combination.

The deficiencies of the Linsley et al references are not cured by Newman et al or Applicants' admissions. Applicants acknowledge that prior to the present invention the concept of humanizing, chimerizing, or primatizing antibodies in order to reduce immunogenicity had been known in the art. Also, it is acknowledged that this had been known in the context of designing therapeutic antibodies. However, this further does not render the claimed invention unpatentable as the references separately or in combination do not teach or suggest a monoclonal antibody

having the claimed binding characteristics. Therefore, withdrawal of the §103 rejection based on the Linsley et al references taken in view of Applicants' admissions, art-known procedures, and Newman et al, *Biotechnology*, 1992, is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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October 14, 1997